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Formulation and evaluation of sustained release matrix tablets of glipizide

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Abstract
Sustain release with the introduction of matrix tablets have proved to be an effective tool to control the release of drug without involving the complex production procedures. Matrix tablets are one of the most widely used oral controlled –release systems containing a therapeutic agent, homogeneously dissolved or dispersed, in a compressed water-swellable core. Interactions between water, polymer, and drug are the primary factors for controlled release, various formulation variables, such as polymer grade, drug/polymer ratio, drug solubility, and drug and polymer particle size can influence drug release rate to a greater or lesser degree. One of the most important stages in the formulation process is the selection of the polymeric matrix formers. Glipizide was selected as a candidate for developing sustained release matrix tablet. An attempt was made to prepare inclusion complexes with β -cyclodextrin. The major objective of the present study is to formulate and evaluate sustained release matrix tablets of Glipizide-β-cyclodextrin complexes using hydrophilic polymers in view to sustain the drug release. Glipizide-β-cyclodextrin complexes were prepared by employing kneading technique and characterized by FT-IR and DSC. Matrix tablets of Glipizide-β-cyclodextrin complex were prepared by direct compression method. The compressed matrix tablets were evaluated for the tablet properties using official procedures.

Keywords: Matrix tablets, Glipizide, β-cyclodextrin

Introduction
Effective therapeutic concentration can be achieved by the sustained release method in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous sustain release oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs. However generating such a system requires certain consideration of which the half life and the pharmacological action of the drug form an essential part. In many instances, conventional method is more preferred to deliver the drug, but some drugs are unstable and toxic by frequently dosing. These kinds of drug have narrow therapeutic range and face solubility difficulties. In such cases, sustained drug delivery system is used, which maintain the drug plasma level in the therapeutic index [1, 4].

Most of sustained release dosage form follows the mechanism of diffusion, dissolution or combination of both, to produce slow release of drug at predetermined rate. Hypothetically, a sustained release dosage form should release the drug by a zero-order mechanism which maintains drug plasma level time similar to intravenous infusion [5]. Matrix tablets are one of the most widely used oral controlled–release systems containing a therapeutic agent, homogeneously dissolved or dispersed, in a compressed water-swellable core. The mechanism of drug release from polymeric matrices involves solvent penetration, hydration and swelling of the polymer, diffusion of the dissolved drug in the matrix, and erosion of the gel layer. Initially, the diffusion co-efficient of the drug in the dehydrated hydrogel is very low, but increases significantly as the gel imbibes water. Interactions between water, polymer, and drug are the primary factors for controlled release, various formulation variables, such as polymer grade, drug/polymer ratio, drug solubility, and drug and polymer particle size can influence drug release rate to a greater or lesser degree [6, 7].

Material and methods
Preparation of Glipizide-β-Cyclodextrin Complexes
Physical mixture
Physical mixture was prepared by simple mixing of 1:1 molar ratio of drug and β- cyclodextrin. The physical mixture was stored in a dessicator before used.

Kneading method
Glipizide and β-cyclodextrin in 1:1 M ratios were triturated in a mortar with 10 ml of distilled water. The thick slurry was kneaded for 45 minutes and dried at 55 °C. The kneaded product was passed through mesh no 100 and stored in desiccators.

Formulation of sustained release matrix tablets containing Glipizide / Glipizide-β-CD-complex
The matrix tablets of Glipizide/Glipizide -β- cyclodextrin complex were prepared employing HPMC K4 M as a matrix former by direct compression method.

1. The ingredients consisting of Glipizide / Glipizide-β-CD-complex, hydroxypropyl methyl cellulose, sodium carboxy methyl cellulose, microcrystalline cellulose (Avicel) were passed through a sieve no. 60 separately and mixed for 30 min in a plastic bag to obtain a uniform blend.
2. The blend was lubricated with 2 % w/w talc and 1% w/w magnesium stearate.
3. The lubricated blend was compressed in to matrix tablets.
4. The composition of a matrix tablets of Glipizide / Glipizide-β-CD-complex are shown in Table-1.
5. The compressed matrix tablets were evaluated for the tablet properties using official procedures

Table 1: Composition of Matrix tablets (Theoretical weight of each tablet: 200 mg)

Formulation Code	Glipizide	Glipizide βCD complex	HPMC	NaCMC	Avicel	Mg stearate	Talc
F1	10	-	20	20	144	04	02
F2	10	-	40	25	109	04	02
F3	10	-	60	50	74	04	02
F4	10	-	80	-	104	04	02
F5	10	-	100	-	84	04	02
F6	10	-	120	-	64	04	02
F7	-	70	20	20	84	04	02
F8	-	70	40	25	49	04	02
F9	-	70	60	50	14	04	02
F10	-	70	80	-	44	04	02
F11	-	70	100	-	24	04	02
F12	-	70	120	-	4	04	02

Results and discussion

Characterization of API

Glipizide was found to be white colored powder with no odor. The melting point of Glipizide by capillary tube method was found to be 208± 1.27˚C. UV spectroscopy scanning of glipizide in PBS pH 7.4 and 0.1N NaOH showed peak at 276 nm.

Characterization of Glipizide-β- Cyclodextrin complexes

Differential Scanning Calorimetry

The thermogram of Glipizide showed a sharp endothermic peak at 212°C.whereas β- Cyclodextrin exhibited a very broad endothermal phenomenon between 100°C and 140°C. A low intensity peak characteristic of Glipizide appeared at 212°C in the thermograms of physical mixture and complexes. DSC thermogram of Glipizide displayed a well defined melting point peak at 212°C. The DSC curve of β-Cyclodextrin exhibited a very broad endothermic phenomenon between 100°C and 140°C due to loss of water. The melting point of Glipizide and the dehydration peak of β-cyclodextrin were observed in the thermogram of the physical mixture and the β-Cyclodextrin complexes. The peak intensities in case of the β-Cyclodextrin complexes were much reduced when compared to those in the physical mixture indicating a weak interaction between the drug and β-cyclodextrin probably due to formation of drug-β-cyclodextrin complex. This indicates that there is no interaction between drug and excipients.

Fourier transform Infrared spectroscopy

The IR spectrum of pure Glipizide, physical mixture and Glipizide-β-Cyclodextrin shows that peaks were not affected and prominently observed in FT-IR spectrum. This indicates that there is no interaction between Glipizide and excipients and the drug was compatible with the formulation components.

Evaluation of Blend:

The method adopted for the preparation of Glipizide tablet was directly compressible method. The formula for the preparation of blends was described in Table-1. The blends obtained were evaluated for blend properties and are given in Table-2.

Table 2: Evaluation of blend

Formulations	Angle of Repose	Bulk Density (g/ml)*	Carr's Index (%)*	Hausner ratio*
F1	27.11 ±0.193	0.4554 ±0.039	14.14 ±1.67	1.19 ±0.066
F2	28.50±0.302	0.3776 ±0.068	12.96±1.54	1.13±0.102
F3	29.51 ±0.378	0.4190 ±0.034	16.27 ±1.81	1.19 ±0.035
F4	26.62 ±0.257	0.3830 ±0.046	18.12 ±1.15	1.20 ±0.053
F5	26.24±0.315	0.4329 ±0.037	14.98±1.35	1.17±0.090
F6	27.71 ±0.245	0.3830 ±0.046	15.94 ±1.28	1.18 ±0.045
F7	25.27 ±0.195	0.4055 ±0.036	16.98 ±1.86	1.20 ±0.045
F8	27.01±0.297	0.3741 ±0.045	14.65±1.44	1.17±0.091
F9	29.60 ±0.296	0.4138 ±0.044	16.12 ±1.61	1.19 ±0.056
F10	25.33 ±0.238	0.3750 ±0.040	15.58 ±1.12	1.17 ±0.049
F11	28.15±0.327	0.4308 ±0.050	12.66 ±1.56	1.13±0.025
F12	26.65 ±0.301	0.4444 ±0.036	14.30 ±1.55	1.19 ±0.091

* Mean ± sd., n=3

The angle of repose for the formulated blend was carried out and the results were shown in Table-2 It concludes that the entire formulations blends were found to be in the ranges from 25.27 to 29.60, which indicates good flow property of blends. Carr‘s index was carried out and found to be between14.30% to 16.98%. The results shown in Table-2 indicate the powder blends have the required flow property for compression. Hausner`s ratio was carried out and found to be between 1.17 to 1.20.The results shown in Table-2 indicated the powder blends have good flow properties for compression.

Evaluation of Formulated Tabletss

The average values of thickness, hardness, friability, weight variation Disintegration and drug content uniformity of the matrix tablets containing Glipizide/Glipizide-β-Cyclodextrin complex prepared. The matrix tablets prepared by the direct compression had uniform thickness and hardness. Tablet

thickness was found to range from 3.10 to 3.48 mm whereas tablet hardness was found to range from 3.5 to 4.5 Kg/cm^2.the tablets were found to comply with the official standards of Friability, weight variation test and % drug content uniformity.

Table 3: Tablet properties

Formulation	Thickness (mm) (n = 10)	Hardness (Kg/cm^2)	Friability (%)	Wt. Var.	Drug cont. (n = 20)	Disintegration
F1	3.28 ± 0.13	4.2 ± 0.24	0.24	PASS	9.70 ± 0.35	NO
F2	3.53±0.17	4.3±0.19	0.43	PASS	9.25± 0.30	NO
F3	3.30 ± 0.10	4.1 ± 0.29	0.42	PASS	9.10 ± 0.32	NO
F4	3.45 ± 0.20	4.0 ± 0.29	0.45	PASS	9.70 ± 0.19	NO
F5	3.40±0.15	3.8±0.27	0.40	PASS	9.51± 0.35	NO
F6	3.48 ± 0.14	4.5 ± 0.19	0.32	PASS	8.75 ± 0.24	NO
F7	3.10 ± 0.17	3.5 ± 0.25	0.41	PASS	9.21 ± 0.33	NO
F8	3.31±0.22	4.0±0.24	0.35	PASS	9.30± 0.31	NO
F9	3.16 ± 0.21	4.3 ± 0.30	0.32	PASS	9.50 ± 0.17	NO
F10	3.13 ± 0.19	3.9 ± 0.31	0.36	PASS	9.30 ± 0.2 9	NO
F11	3.60±0.20	4.27±0.25	0.45	PASS	9.65± 0.29	NO
F12	3.15 ± 0.15	4.2 ± 0.32	0.25	PASS	9.81 ± 0.26	NO

* Mean ± sd., n=3

Drug Release Studies:

The dissolution data of the matrix tablet containing Glipizide/Glipizide-β-Cyclodextrin complex are showed in Table 4, 5 and 6 respectively. The cumulative % drug release vs. time plots are showed in Figure 1, 2 and 3. It was observed that all the formulations were found to exhibit a controlled drug release spread over period ranging from 18-24 hrs. Formulation F3 and F12 showed desirable response for 24 hrs.

Table 4: *In-vitro* Dissolution data of F1, F2, F3 and F4

Time(hours)	%CDR±sd.			
	F1	**F2**	**F3**	**F4**
1	29.99±1.222	26.75±1.315	11.67±1.532	21.04±1.222
2	31.18±1.589	33.42±1.121	14.04±1.267	24.88±1.445
3	36.23±1.222	38.01±1.445	15.51±1.266	31.18±1.224
4	40.00±1.765	42.37±1.202	18.66±1.457	35.46±1.004
5	45.09±1.587	48.47±1.305	20.92±1.268	41.55±1.441
6	49.85±1.767	52.15±1.255	24.11±1.478	46.14±1.447
7	54.25±1.382	57.84±1.310	27.69±1.464	49.99±2.387
8	59.30±1.386	64.36±1.615	30.54±1.268	53.37±1.217
9	64.48±1.441	68.05±1.515	32.86 ±1.536	56.33±1.389
10	68.16±1.221	73.74±2.109	36.11±1.807	59.97±1.218
11	72.89±1.223	77.42±2.205	38.92±1.169	64.14±1.229
12	77.65±2.385	81.90±2.305	43.45±1.445	69.92±2.384
13	80.22±2.386	85.58±2.555	47.20±2.689	74.00±2.776
14	84.00±2.587	90.06±3.122	51.45±2.473	78.50±2.451
15	87.24±2.005		56.65±2.445	81.34±2.593
16	90.22±2.448		60.80±2.931	84.46±2.208
17	95.49±2.595		64.18±2.475	86.71±2.678
18	99.47±2.594		67.14±2.276	90.50±2.206
19			69.98±2.437	92.31±3.320
20			73.43±2.386	95.31±3.214
21			77.95±2.284	99.91±2.795
22			80.32±3.233	
23			84.25±3.351	
24			86.90±2.735	

* Mean ± sd., n=3

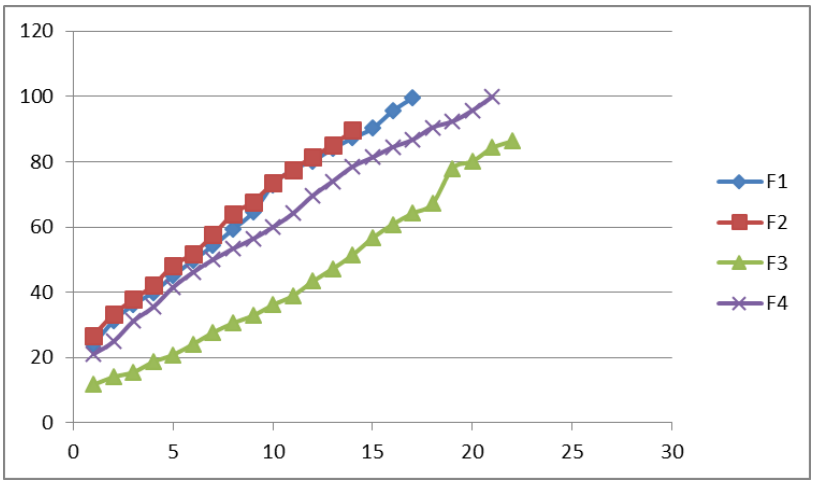

Fig 1: *In-vitro* Dissolution profiles of F1, F2, F3 and F4

Table 5: *In-vitro* Dissolution data of F5, F6, F7 and F8

Time(hours)	%CDR±sd.			
	F5	**F6**	**F7**	**F8**
1	29.19±1.310	6.40±1.426	37.57±1.351	13.30±1.321
2	37.22±1.807	9.14±1.248	49.54±1.211	17.81±1.344
3	41.99±1.691	11.46±1.247	56.14±1.252	23.48±1.675
4	43.92±1.445	12.95±1.430	60.62±1.442	27.13±1.329
5	48.74±1.268	15.30±1.252	67.05±2.276	33.21±1.321
6	53.09±1.478	18.08±1.658	76.32±2.662	39.69±1.463
7	58.64±1.934	21.16±1.419	86.52±2.432	46.17±1.471
8	63.01±2.302	24.28±1.492	93.36±3.495	51.05±1.478
9	70.12±2.689	26.26±1.433	99.81±3.876	55.52±1.793
10	73.93±2.389	28.68±1.653		59.17±1.814
11	76.10±2.442	31.96±1.497		64.02±1.842
12	79.67±2.468	35.55±1.649		67.68±1.871
13	84.03±2.452	39.87±1.651		72.95±2.893
14	86.35±2.873	43.63±2.414		78.22±2.023
15		47.72±2.241		84.73±2.123
16		51.32±2.658		89.97±2.372
17		54.36±2.746		
18		58.20±2.666		
19		61.20±3.342		
20		64.82±2.341		
21		67.86±2.269		
22		69.98±2.432		
23		73.20±2.321		
24		75.65±2.011		

***** Mean ± sd., n=3

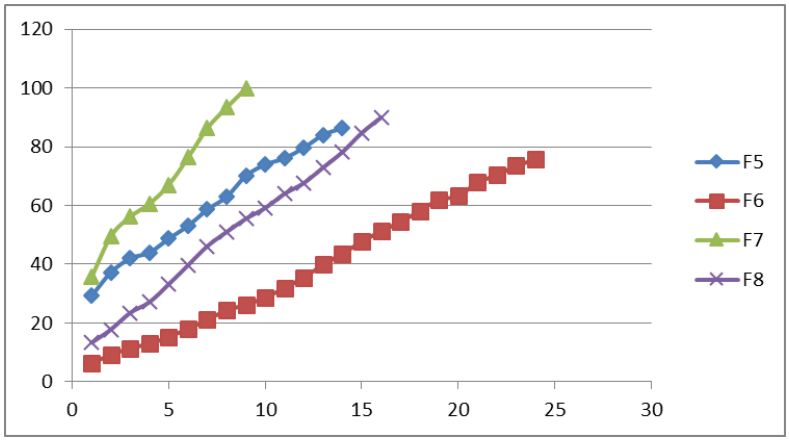

Fig 2: *In-vitro* Dissolution profiles of F5, F6, F7 and F8

Table 6: *In-vitro* Dissolution data of F9, F10, F11 and F12

Time(hours)	%CDR±sd.			
	F9	**F10**	**F11**	**F12**
1	13.36±1.393	31.99±1.231	17.48±1.328	9.51±1.092
2	17.63±1.226	40.73±1.401	21.447±1.342	13.75±1.231
3	19.82±1.930	52.06±1.229	26.53±1.453	16.49±1.246
4	23.57±1.394	57.44±1.464	31.29±1.438	21.15±1.253
5	27.28±1.455	62.84±1.398	35.92±1.473	24.44±1.370
6	32.54±1.233	68.94±1.463	41.77±1.487	28.38±1.453
7	35.86±1.232	74.01±2.323	44.53±1.583	33.61±1.398
8	40.77±1.321	77.75±2.464	48.42±1.653	37.98±1.439
9	44.79±1.387	83.25±4.233	53.67±1.783	42.88±1.543
10	49.39±1.382	91.87±3.658	64.76±1.842	46.67 ± 1.453
11	52.42±1.234	99.72±3.494	67.90±1.864	50.35±1.648
12	56.44±1.233		70.43±2.324	53.16±1.874
13	61.86±1.362		74.96±2.453	57.25±1.789
14	65.46±1.389		76.98±2.652	62.12±1.753
15	70.01±1.769		78.13±2.587	66.64±1.849
16	75.62±2.137		82.81±2.783	70.08±1.883
17	80.18±2.243		83.40±3.204	73.85±2.045
18	84.45±2.283		87.49±3.353	77.75±1.893
19	88.56±2.323			78.2±1.879
20	92.43±2.731			82.82±1.743
21	99.73±3.768			86.65±1.874
22				87.36±2.149
23				91.80±2.537
24				96.32±2.320

* Mean ± sd., n=3

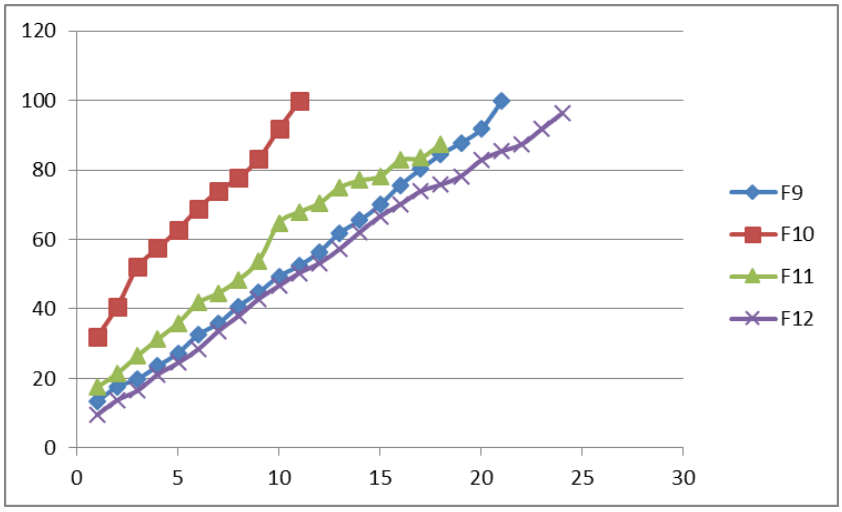

Fig 3: *In-vitro* Dissolution profiles of F9, F10, F11 and F12

Stability Studies

Accelerated Stability Study

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic, and toxicological specifications. Tablets of F3 and F12 were kept for accelerated stability study at 40±2 ºC and 75±5% RH for 45 days in the stability chamber. After a period of one month, the samples were observed for any change in physical parameters It was observed that surface was devoid of any change in colour or appearance of any kind of spots on it. It was also noted that surface was free of any kind of microbial or fungal growth or bad odour. No changes in the smoothness of the tablets were noted. The formulations were found to be stable in terms of drug content and dissolution stability as shown in Table-7.

Table 7: Characteristic of Glipizide and Glipizide-β-Cyclodextrin complex tablets after 1 month Formulations

Parameters	**F3**	**F12**
Hardness (Kg/cm^2)	4.2 ± 0.13	4.3 ± 0.12
Content Uniformity	9.10 ± 0.02	9.81 ± 0.02
In vitro release	86.90±0.735	96.32±1.352

By comparison, it was found that after a period of one month of storage there were no changes in the physical as well as drug

release profiles of the tablets of optimize batch and was imitating the same drug release pattern.

Conclusion

Glipizide is a second-generation sulphonyl urea derivative used to treat type-2 diabetes. According to the biopharmaceutical classification scheme the drug belongs to class II owing to its high gastro intestinal permeability. Due to its short half-life, frequent administration and chronic usage Glipizide was selected as a candidate for developing sustained release matrix tablet. Since the drug known to exhibit a poor aqueous solubility an attempt was made to prepare inclusion complexes with β-cyclodextrin. A sustained release formulation was employed to design sustained release matrix tablet by direct compression technique. By optimizing the setting of the polymer levels matrix tablet with good sustained released and tablet properties were obtained.

Core tablets of Glipizide (F3) and Glipizide-β-cyclodextrin complex (F12) formulations were successfully prepared by direct compression. The core tablets were evaluated for pharmacopoeial and non-pharmacopoeial tests. Based on the results, F3 and F12 were identified as better formulations among the developed formulations. Glipizide and Glipizide-β-cyclodextrin complex formulations F3 and F12 were passed all official and unofficial tests. *In vitro* release profile of optimized formulation of Glipizide and Glipizide-β-cyclodextrin complex tablets F3 and F12 were found to be all most similar to each other but F12 showed better result up to 96%. Developed formulations were found to be stable after one month of storage at accelerated stability conditions. It can be concluded that formulation F3 and F12 showed desirable response but both of them the F12 is optimized formulation. All formulations can be obtained with minimum expenditure of time and money.

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